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EXAMINER
PORTNER, VIRGINIA ALLEN

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No. 09/821,348	Applicant(s) Singh et al
	Examiner Portner	Art Unit 1645

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 18, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above, claim(s) *2-11* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-11* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-11 are pending.

Claim 1 is under consideration.

Election/Restriction

1. Applicant's election with traverse of Group I, (Claim 1, drawn to a recombinant protein, classified in class 424, subclass 203.1), in Paper No. 11 is acknowledged. The traversal is on the ground(s) that "the search of all of the claims is not "a serious burden, as required, "the claims grouped separately are not independent and distinct and therefore, the examination of the entire application cannot constitute a serious burden. These arguments have been fully considered but are not found to be persuasive for the reasons below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1)independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the inventions of Groups I-IV are drawn to distinct inventions which are related as separate products capable of separate functions. Restrictions between the inventions is deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. In the instant case a burden has been established in showing that the inventions

of Groups I-IV are classified separately necessitating different searches of issued US Patents. However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example genes and chimeric proteins and inhibitors of natural proteins differ structurally, and functionally from one another. Additionally, it is submitted that the inventions of Groups I-IV have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group. For these reasons the restriction requirement is deemed to be proper and is therefore made Final.

2. Claims 2-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups II-IV, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Claim Objections

3. Claim 1 is objected to because of the following informalities:

a. Claim 1 recites the ~~phase~~ phrase 'iota b toxin'; what is intended by the recitation of a phrase in quotes ' ' is unclear. Claim 1 also recites various abbreviations: PA-1; PA; and 2B2-2B3 loop. What the meanings of these abbreviations are, is unclear. ~~Clarification~~ The objection could be obviated by amendment of the claim to recite the meaning of the recited letters or a master sequence in which the loop resides.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instantly claimed invention is directed to a genus of novel molecules. With the exception of SEQ ID NO: 2 which encodes a specific derivative of the naturally occurring iota b toxin 2B2-2B3 loop which is in association with the entire protective antigen molecule which results in a recombinant protein of about 85.2 kilodaltons (see instant specification Figure 1), the skilled artisan cannot envision the detailed structure of the recombinant protein with the recited functional characteristics. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Only SEQ ID Nos: 2 has been described, therefore the written description has not set forth a representative number of species of invention to enable the claimed genus of recombinant proteins drawn to "a novel molecule useful for anthrax toxin inhibition in vivo comprising a recombinant protein designated PA-1".

PA-1 is not described by structure correlated by function, but only through the functional recitation of claim limitations "anthrax toxin inhibition in vivo", and "dominant negative inhibitor

of PA". PA-1 is required to comprise "amino acid residues of the amphipathic loop of the homologous toxin iota". The specific amino acid residues from the homologous toxin iota of the recombinat protein has not been defined to comprise any specific number, size or sequence other than that of SEQ ID NO 2, and all of SEQ ID No 2 is not required to be apart of the claimed "novel molecule" in light of the fact that the claimed recombinant protein need only comprise "amino acid residues" of SEQ ID NO 2.

The specification does not provide written descriptive support for the claimed invention directed to a genus of "novel molecule" that function as inhibitors, as only "an amino acid sequence of SEQ ID NO 2" has been described and all of the variants of SEQ ID NO 2 that only comprise "amino acid residues of the amphipathic loop of the homologous toxin iota" have not been set forth in the instant specification. Within the scope of the claimed invention are molecules that have no shared biological function, are structural homologs, or allelic variants of SEQ ID No 2. SEQ ID NO 2 is not a native sequence of iota toxin b, as the sequence disclosed in Swiss-prot, differs from that recited in claim 1. Claim 1 requires the amino acid residues to be from "the homologous toxin iota", and sets forth a sequence that is not native to "iota b toxin" or iota toxin Ia.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

A recombinant protein is encoded by a recombinant nucleic acid molecule. Consistent with this fact, the court held in the decision *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

There is insufficient evidence to support the generic claims as provided by the Interim Written Description Guild lines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore only a recombinant protein of about 85.2 kDa, which

comprises Anthrax protective antigen with a 2B2-2B3 loop of SEQ ID NO 2, and functions as a dominant negative inhibitor of anthrax toxin in vivo, has been disclosed and described, but not the full breadth of the claims meets the written description provision of 35 U.S.C. 112, first paragraph.

5. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the term "PA". While protective antigen for anthrax toxin is known, various forms of this toxin are also known to exist, specifically an 83 kDa protein, a 63 kDa protein and a 20 kDa protein (see US Pat. 6592872, Brief Summary, col. 2, lines 13-27; and Swiss-Prot accession number P13423 which teaches Protective antigen to contain PA-83, PA-63 and PA-20). What portion of the protective antigen is intended in the claims through the broad recitation of the term PA?

Claim 1 recites the phrase "wherein the 2B2-2B3 loop"; this phrase lacks antecedent basis in claim 1 which is not required to comprise a 2B2-2B3 loop. Clarification of the invention to comprise a 2B2-2B3 loop could obviate this rejection through providing antecedent basis for this phrase.

Claim 1 recites the phrase "homologous toxin iota". While iota toxin is known, there are two iota toxin components, Ia and Ib. The homologous toxin iota reads on both Ia and Ib components of iota toxin. Claim 1 recites an amino acid sequence which is not present in either of iota toxin Ia or Ib. Clarification, of the meaning of the phrase "homologous toxin iota" relative

to the required amino acid residues which are not specifically specified, an must function as an inhibitor, is requested.

Claim 1 recites "(SEQ ID NO:2). SEQ ID NO 2 is defined by the recited sequence of amino acids, but upon consideration of that master sequence of iota toxin beta (iota-b) of Clostridium perfringens in Swiss Prot, the amino acids from positions 302 to 324 did not correspond to the amino acids recited in claim 1. Amino acids 336-355 of Clostridium perfringens toxin iota component Ib (accession number Q46221) corresponded to a portion of SEQ ID NO 2 recited in claim 1, but there were three amino acids that differ between the deposited reference amino acid sequence in Swiss-Prot and the sequence of the claims, specifically "AGF". The amino acid sequence "AGF" is not naturally found in iota toxin b , and are recited in the sequence of the claims. No apparent correspondence for all of SEQ ID NO 2, of the claims, could be found relative to a known sequence for iota toxin component Ib, or accession number Q46221 (Iota toxin B component). What the other amino acids are from 1-302 and any other amino acids of the loop of iota B toxin of claim 1 are unclear, as no parent amino acid sequence which is known to comprise SEQ ID NO 2. Therefore the recitation of a range of amino acids that does not correspond to any specific known reference sequence introduces confusion into the claims. Absent a master sequence into which the recited sequence (SEQ ID NO 2) is extracted, the recited numbering of the amino acids is unclear.

Claim 1 recites the designated term "PA-1". The inhibitor of anthrax toxin is functionally defined to be a "dominant negative inhibitor of PA", but what the overall sequence of the recombinant protein PA-1 is, is not distinctly claimed. Only SEQ ID NO 2 is recited in the claim, which requires at least a portion of iota toxin Ib component. No master sequence for the iota Ib toxin is provided and what additional structural components the recombinant PA-1 inhibitor

comprises is not distinctly claimed based upon only functional limitations being set forth to define the PA inhibitor. Critical amino acids that provide for the recited function are missing from the claim. Clarification of what the recombinant protein PA-1 comprises other than SEQ ID No 2, is requested.

Claim 1 recites the phase " 'iota b toxin' sequence inserted a 2B2-2B3 loop in the recombinant PA-1 : (SEQ ID NO 2)^{302} V G V S I S A G Y Q N G F T G N I T T S A G F ^{324}. Is PA-1 SEQ ID NO 2? Or is the 'iota b toxin' sequence inserted into ^{302} V G V S I S A G Y Q N G F T G N I T T S A G F ^{324}? Would SEQ ID NO 2 alone form a loop? No additional structural components are recited in the claim to define the loop into which the iota B toxin sequence is inserted. SEQ ID No 2 is not a native iota B toxin sequence, nor is SEQ ID NO 2 a native anthrax toxin sequence. Is an additional sequence inserted into ^{302} V G V S I S A G Y Q N G F T G N I T T S A G F ^{324} ? What is inserted? What amino acid residues is SEQ ID NO 2 associated based upon the recited preamble of the claim? Clarification is requested.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Sirard et al (June 1997).

Sirard et al discloses the instantly claimed invention directed to a recombinant protein that comprises "amino acid residues of the amphipathic loop of the homologous toxin iota", wherein

the recombinant protein of Sirard et al is a recombinantly produced iota toxin Ib component , which was produced through the fusion of Bacillus anthraces *pag* gene promoter to the iota toxin Ib gene (see page 2029, col. 2, paragraph 2; page 2030, col. 1, paragraph 5).

The recombinant protein comprised a 2B2-2B3 loop, as the recombinant protein was the entire iota toxin Ib component and would inherently comprise at least a portion of the [redacted] amino acid sequence of SEQ ID NO 2 (96 kDa form, see page 2030, paragraph 5).

The recombinant protein served to induce a protective immune response that was useful for inhibition of the toxin in vivo (see page 2032, col. 1, paragraphs 2-4; see title, abstract, page 2029, col. 1, paragraph 1 where PA antigen is defined to be encoded by "pag" gene, and page 2029, col. 2, paragraph 2, where the article defines "a gene fusion between the pag gene promoter and the *ibp* gene, encoding Ib") which is directed to a homolog toxin of PA, specifically iota toxin Ib, and comprises amino acid residues of SEQ ID NO 2. The reference anticipates the instantly claimed invention in light of the combination of claim limitations set forth in claim 1 that are unclear (see rejection of claim 1 under 35 U.S.C. 112, second paragraph) and read on the disclosure of Sirard et al.

8. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Sellman et al (March 16, 2001).

Sellman et al disclose a dominant negative mutant inhibitor of PA, wherein the molecule comprises an amino acid residue present in the 2B2-2B3 loop of iota toxin Ib, specifically an

"A(alanine)" which is present in SEQ ID NO 2, wherein the dominant negative mutant inhibitor of PA evidenced a mutation with a change from phenylalanine to alanine (see page 8376, col. 1, paragraph 5, and col. 2, paragraph 1). The dominant negative mutant inhibitor of PA was derived from PA63, functioned to co-oligomerize with wildtype PA63, but the resulting hetero-oligomers were unable to mediate translocation into host cells, thus defining the capability of the molecule to inhibit anthrax toxin in vivo (see page 8376, col. 1, last two sentences). The molecule was not designated as PA-1, but evidenced the functional characteristics recited in the claims and was referred to and evidenced the capability of being a dominant negative mutant inhibitor of PA.

Inherently the reference anticipates the instantly claimed invention.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
10. Cirino et al (US Pat. 6,329,156); Leppla et al (US Pat. 5,591,631); Orcutt (US Pat. 4,264,588) are cited to show anthrax and iota toxins.
11. Billington et al (1998); Marvaud et al (2001) and Stiles et al (2000) are cited to show Clostridium perfringens toxins.
12. Petosa, C et al (1997) and Price, LB et al (1999) are cited to show Bacillus anthracis protective antigen.

13.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242. The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp September 10, 2003

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